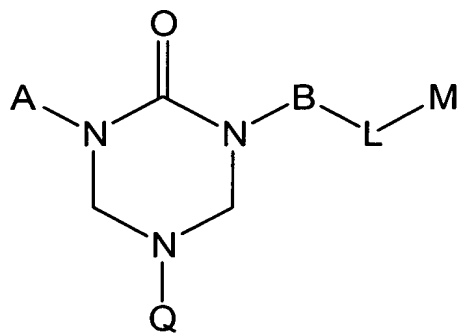


**2005 0032798**

1. A compound of formula I,



or a pharmaceutically acceptable salt thereof,

wherein

A and B are, independently, 5-10 membered cyclic moieties which are optionally substituted with 1-4 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_pR^1$ ,  $SO_2NR^1R^2$ ,  $C(O)NR^1R^2$ ,  $C(NR^1)R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro, and A is additionally  $C_3$  to  $C_6$  linear or branched alkyl;

L is a bridging group selected from the group consisting of:

- (a)  $-(CH_2)_m-O-(CH_2)_l-$ ,
- (b)  $-(CH_2)_m-(CH_2)_l-$ ,
- (c)  $-(CH_2)_m-C(O)-(CH_2)_l-$ ,
- (d)  $-(CH_2)_m-NR^3-(CH_2)_l-$ ,
- (e)  $-(CH_2)_m-NR^3C(O)-(CH_2)_l-$ ,
- (f)  $-(CH_2)_m-S-(CH_2)_l-$ ,
- (g)  $-(CH_2)_m-C(O)NR^3-(CH_2)_l-$ ,
- (h)  $-(CH_2)_m-CF_2-(CH_2)_l-$ ,
- (i)  $-(CH_2)_m-CCl_2-(CH_2)_l-$ ,
- (j)  $-(CH_2)_m-CHF-(CH_2)_l-$ ,
- (k)  $-(CH_2)_m-CH(OH)-(CH_2)_l-$ ;
- (l)  $-(CH_2)_m-C \equiv C-(CH_2)_l-$ ; and
- (m)  $-(CH_2)_m-C=C-(CH_2)_l-$ ;

wherein m and l are integers independently selected from 0-4,

M is

- (i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, and nitro;
- (ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, and nitro;
- (iii) 5 and 6 membered monocyclic heteroaryl, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, nitro and oxides;
- (iv) 8 to 10 membered bicyclic heteroaryl, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, nitro and oxides;
- (v) saturated and partially saturated  $C_3$ - $C_7$  monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, and nitro;
- (vi) saturated and partially saturated  $C_5$ - $C_{12}$  bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, and nitro;
- (vii) saturated and partially saturated 5 to 7 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, nitro and oxides (e.g. =O,  $-O^-$  or  $-OH$ ); or
- (viii) saturated and partially saturated 7 to 12 membered bicyclic heterocyclic moiety, having 1-6

heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, nitro and oxides; and

each  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and Q is, independently,

(a) hydrogen,

(b)  $C_1$ - $C_5$  linear, branched, or cyclic alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl, up to perhalo substituted  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_3$  alkoxy, hydroxy, carboxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

(c) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl, up to perhalo substituted  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_3$  alkoxy, hydroxy, carboxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

(d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl, up to perhalo substituted  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_3$  alkoxy, hydroxy, carboxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

(e)  $C_1$ - $C_3$  alkyl-phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl, up to perhalo substituted  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_3$  alkoxy, hydroxy, carboxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

(f)  $C_1$ - $C_3$  heteroaryl-alkyl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl, up to perhalo substituted  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_3$  alkoxy, hydroxy, carboxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and

nitro; or

(g) up to per-halo substituted C<sub>1</sub>-C<sub>5</sub> linear, branched or cyclic alkyl and when not perhalo substituted, optionally substituted with 1-3 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, up to perhalo substituted C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, hydroxy, carboxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro.

2. A compound as in claim 1 wherein A is

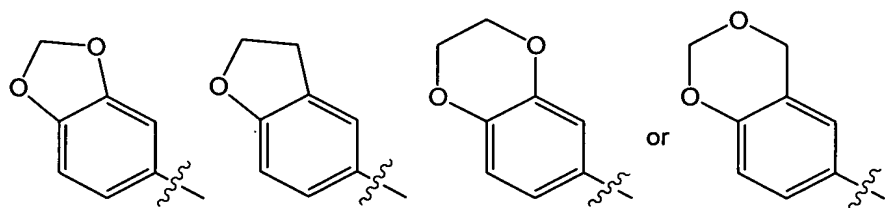
(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R<sup>1</sup>, OR<sup>1</sup>, NR<sup>1</sup>R<sup>2</sup>, S(O)<sub>p</sub>R<sup>1</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, C(O)NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>C(O)R<sup>2</sup>, NR<sup>1</sup>C(O)OR<sup>2</sup>, halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R<sup>1</sup>, OR<sup>1</sup>, NR<sup>1</sup>R<sup>2</sup>, S(O)<sub>p</sub>R<sup>1</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, C(O)NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>C(O)R<sup>2</sup>, NR<sup>1</sup>C(O)OR<sup>2</sup>, halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R<sup>1</sup>, OR<sup>1</sup>, NR<sup>1</sup>R<sup>2</sup>, S(O)<sub>p</sub>R<sup>1</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, C(O)NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>C(O)R<sup>2</sup>, NR<sup>1</sup>C(O)OR<sup>2</sup>, halogen, cyano, and nitro;

(iv) 8 to 10 membered bicyclic heteroaryl, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R<sup>1</sup>, OR<sup>1</sup>, NR<sup>1</sup>R<sup>2</sup>, S(O)<sub>p</sub>R<sup>1</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, C(O)NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>C(O)R<sup>2</sup>, NR<sup>1</sup>C(O)OR<sup>2</sup>, halogen, cyano, and nitro; or

(v) a group of the formula



optionally substituted with 1-4 substituents independently selected from the group consisting of R<sup>1</sup>, OR<sup>1</sup>, NR<sup>1</sup>R<sup>2</sup>, S(O)<sub>p</sub>R<sup>1</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>2</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, C(O)NR<sup>1</sup>R<sup>2</sup>, NR<sup>1</sup>C(O)R<sup>2</sup>,

$\text{NR}^1\text{C}(\text{O})\text{OR}^2$ , halogen, cyano, and nitro.

3. A compound as in claim 1 wherein B is

- (i) phenyl or naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $\text{C}_1\text{-C}_5$  linear or branched alkyl,  $\text{C}_1\text{-C}_5$  linear or branched haloalkyl up to perhalo,  $\text{C}_1\text{-C}_3$  alkoxy,  $\text{C}_1\text{-C}_3$  haloalkoxy up to per haloalkoxy, hydroxy, amino,  $\text{C}_1\text{-C}_3$  alkylamino,  $\text{C}_1\text{-C}_6$  dialkylamino, halogen, cyano, and nitro; or
- (ii) 5-6 membered monocyclic heteroaryl groups, having 1-4 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of  $\text{C}_1\text{-C}_5$  linear or branched alkyl,  $\text{C}_1\text{-C}_5$  linear or branched haloalkyl up to perhalo,  $\text{C}_1\text{-C}_3$  alkoxy,  $\text{C}_1\text{-C}_3$  haloalkoxy up to per haloalkoxy, hydroxy, amino,  $\text{C}_1\text{-C}_3$  alkylamino,  $\text{C}_1\text{-C}_6$  dialkylamino, halogen, cyano, and nitro.

4. (Currently Amended) A compound as in claim 1 wherein B is phenyl, naphthyl, or pyridyl, optionally substituted with 1-4 substituents independently selected from the group consisting of  $\text{C}_1\text{-C}_5$  linear or branched alkyl,  $\text{C}_1\text{-C}_5$  linear or branched haloalkyl,  $\text{C}_1\text{-C}_3$  alkoxy, hydroxy, amino,  $\text{C}_1\text{-C}_3$  alkylamino,  $\text{C}_1\text{-C}_6$  dialkylamino, halogen, cyano, and nitro.

5. A compound as in claim 1, where M is

- (i) 5 and 6 membered monocyclic heteroaryl, having at least one nitrogen atom, optionally substituted with 1-3 substituents independently selected from the group consisting of  $\text{R}^4$ ,  $\text{OR}^4$ ,  $\text{NR}^4\text{R}^5$ ,  $\text{S}(\text{O})_q\text{R}^4$ ,  $\text{SO}_2\text{NR}^4\text{R}^5$ ,  $\text{C}(\text{O})\text{NR}^4\text{R}^5$ ,  $\text{C}(\text{NR}^4)\text{R}^5$ ,  $\text{NR}^4\text{SO}_2\text{R}^5$ ,  $\text{C}(\text{O})\text{R}^4$ ,  $\text{C}(\text{O})\text{OR}^4$ ,  $\text{NR}^4\text{C}(\text{O})\text{R}^5$ ,  $\text{NR}^4\text{C}(\text{O})\text{OR}^5$ , halogen, cyano, nitro and oxides;
- (ii) 8 to 10 membered bicyclic heteroaryl, having at least one nitrogen atom, optionally substituted with 1-3 substituents independently selected from the group consisting of  $\text{R}^4$ ,  $\text{OR}^4$ ,  $\text{NR}^4\text{R}^5$ ,  $\text{S}(\text{O})_q\text{R}^4$ ,  $\text{SO}_2\text{NR}^4\text{R}^5$ ,  $\text{C}(\text{O})\text{NR}^4\text{R}^5$ ,  $\text{C}(\text{NR}^4)\text{R}^5$ ,  $\text{NR}^4\text{SO}_2\text{R}^5$ ,  $\text{C}(\text{O})\text{R}^4$ ,  $\text{C}(\text{O})\text{OR}^4$ ,  $\text{NR}^4\text{C}(\text{O})\text{R}^5$ ,  $\text{NR}^4\text{C}(\text{O})\text{OR}^5$ , halogen, cyano, nitro and oxides (e.g.  $=\text{O}$ ,  $-\text{O}^-$  or  $-\text{OH}$ );
- (iii) saturated and partially saturated 5 to 7 membered monocyclic heterocyclic moiety, having at least one nitrogen atom, optionally substituted with 1-3 substituents independently selected from the group consisting of  $\text{R}^4$ ,  $\text{OR}^4$ ,  $\text{NR}^4\text{R}^5$ ,  $\text{S}(\text{O})_q\text{R}^4$ ,  $\text{SO}_2\text{NR}^4\text{R}^5$ ,  $\text{C}(\text{O})\text{NR}^4\text{R}^5$ ,  $\text{C}(\text{NR}^4)\text{R}^5$ ,  $\text{NR}^4\text{SO}_2\text{R}^5$ ,

$C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, nitro and oxides (e.g.  $=O$ ,  $-O^-$  or  $-OH$ ); or

(iv) saturated and partially saturated 7 to 12 membered bicyclic heterocyclic moiety, having at least one nitrogen atom, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, nitro and oxides.

6. A compound as in claim 1, wherein M is optionally substituted pyridine, quinoline, morpholine, indazole, isoquinoline, pyrimidine, or benzimidazole.

7. A compound as in claim 1, wherein A is optionally substituted furyl, thienyl, thiadiazolyl, pyrrolyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, quinolyl, indazolyl, benzimidazolyl, phenyl, tetrahydro-4H-benzo[1,3]dioxinyl or naphthyl.

8. A compound as in claim 1 wherein A is optionally substituted furyl, thienyl, thiadiazolyl, pyrrolyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, quinolyl, isoquinolyl, indazolyl, benzimidazolyl, phenyl, tetrahydro-4H-benzo[1,3]dioxinyl or naphthyl, and  
B is optionally substituted phenyl, naphthyl, quinolyl, or pyridyl.

9. A compound as in claim 1 wherein B is optionally substituted by one or more of methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, i-propyl, t-butyl, methoxy, ethoxy, propoxy, Cl, Br, F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino or diethylamino.

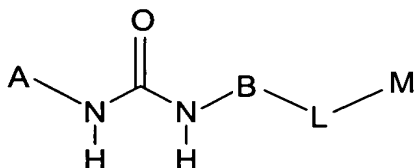
10. A compound as in claim 1 wherein A is optionally substituted by one or more of methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, *tert*-butyl, *sec*-butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, 4-methyl-phenyl, methoxy, ethoxy, propoxy, Cl, Br, F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino or diethylamino.

11. A compound as in claim 1 where L is -O- and M is optionally substituted morpholine, pyridine, quinoline, isoquinoline, benzimidazole, indazole, or pyrimidine.

12. A compound as in claim 1 wherein  
A is optionally substituted phenyl or tetrahydro-4H-benzo[1,3]dioxinyl,  
B is phenyl or naphthyl, optionally substituted with halogen,  
L is -O-,  
and M is optionally substituted pyridine, quinoline, isoquinoline, benzimidazole, indazole, or pyrimidine.

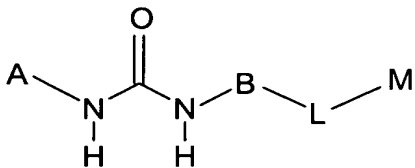
13. A compound as in claim 1 wherein  
A is optionally substituted pyrazolyl,  
B is phenyl or naphthyl, optionally substituted with halogen,  
L is  $-(CH_2)_m-O-(CH_2)_l-$ , and M is morpholine.

14. A compound which releases a urea of the formula



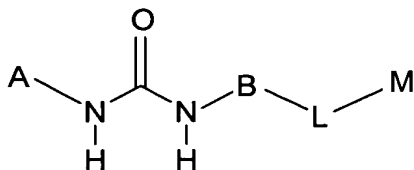
when administered to a patient, wherein A, B, L and M are as defined in claim 1.

15. A compound as in claim 1 which releases a urea of the formula



when administered to a patient.

16. A compound as in claim 2 which releases a urea of the formula



when administered to a patient.

17. A compound is in claim 1 which releases N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyl oxy)-2-fluoro-phenyl) urea, or N-(6-(2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxinyl))-N'-(4-(2-cyano-4-pyridyloxy) phenyl) urea, when administered to a patient.

18. A compound as in claim 1

wherein A is 2-(4-methyl-phenyl)-5-*tert*-butyl-2H-pyrazole-3-yl, B is naphthyl, L is -O-(CH<sub>2</sub>)<sub>2</sub>- and M is morpholine, which releases 1-(5-*tert*-butyl-2-(4-methyl-phenyl)-2H-pyrazole-3-yl)-3-[4-(2-morpholinylethoxy)naphthalene-1-yl]urea when administered to a patient.

19. A compound as in claim 1

wherein A is 3-trifluoromethyl-4-chloro-phenyl, B is phenyl, L is -O- and M is 2-methylcarbamoyl-pyridine-4-yl, which releases N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea when administered to a patient.

20. A compound which is:

- 1-(4-chloro-3(trifluoromethyl)phenyl)-3-(4-(2-(N-methylcarbamoyl)-4-(pyridyloxy)phenyl)-2-oxo-(1,3,5-perhydrotriazapine)



- -{4-[3-(4-chloro-3-trifluoromethyl-phenyl)-5-(2-methoxy-ethyl)-2-oxo-[1,3,5]triazinan-1-yl]-3-fluoro-phenoxy}-pyridine-2-carboxylic acid methylamide
- 4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl)-5-(2-hydroxy-ethyl)-2-oxo-[1,3,5]triazinan-1-yl]-3-fluoro-phenoxy}-pyridine-2-carboxylic acid methylamide
- 4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl)-5-(3-hydroxy-propyl)-2-oxo-[1,3,5]triazinan-1-yl]-3-fluoro-phenoxy}-pyridine-2-carboxylic acid methylamide
- 4-{3-fluoro-4-[5-methyl-2-oxo-3-(2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxin-6-yl)-[1,3,5]triazinan-1-yl]-phenoxy}-pyridine-2-carbonitrile or
- 4-{3-fluoro-4-[5-methyl-2-oxo-3-(2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxin-6-yl)-[1,3,5]triazinan-1-yl]-phenoxy}-pyridine-2-carboxylic acid methylamide

21. The compound which is 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl)-2-oxo-(1,3,5-perhydrotriazapine) which releases N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea (BAY 43-9006) when administered to a patient.

22. A pharmaceutical composition with an effective amount of at least one compound of claim 1 and a physiologically acceptable carrier.

23. A method for treating or preventing a hyper-proliferative disorder in a human or other mammal comprising administering to a human or other mammal in need thereof a compound of claim 1.

24. A method for treating or preventing a hyper-proliferative disorder in a human or other mammal comprising administering to a human or other mammal in need thereof a compound of claim 1 and an additional anti-proliferative agent.

25. A method for treating or preventing a hyper-proliferative disorder in a human or other mammal comprising administering to a human or other mammal in need thereof a compound of claim 1 and a cytotoxic agent or cytostatic chemotherapeutic agent.

26. A method for treating or preventing a disease in a human or other mammal regulated by tyrosine kinase, associated with an aberration in the tyrosine kinase signal transduction pathway, comprising administering to a human or other mammal in need thereof a compound of claim 1.

27. A method for treating or preventing a disease in a human or other mammal mediated by the VEGF-induced signal transduction pathway, comprising administering to a human or other mammal in need thereof a compound of claim 1.

28. A method for treating or preventing a disease in a human or other mammal characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to a human or other mammal in need thereof a compound of claim 1.

29. A method for treating or preventing a disease in a human or other mammal characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to a human or other mammal in need thereof a compound of claim 1, a salt form of a compound of claim 1, simultaneously with another angiogenesis inhibiting agent in the same formulation or in separate formulations.

30. A method for treating or preventing one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a bolus disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis,  
comprising administering to a human or other mammal in need thereof a compound of claim 1.

31. A method for treating or preventing one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a

bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis in combination with another condition selected from the group consisting of:

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) and complications due to total hip replacement,

comprising administering to a human or other mammal in need thereof a compound of claim 1.

32. A method for treating or preventing one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

in combination with an infectious disease selected from the group consisting of :

tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli*

infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV),

comprising administering to a human or other mammal in need thereof a compound of claim

I.

33. A method for treating or preventing a disease in a human or other mammal mediated by the VEGF-induced signal transduction pathway comprising administering the compound 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl)-2-oxo-(1,3,5-perhydrotriazapine).

34. A method for treating or preventing a disease in a human or other mammal administering the compound 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl)-2-oxo-(1,3,5-perhydrotriazapine).

35. A method for treating or preventing p38 mediated diseases, comprising administering a compound of formula I wherein A is 2-(4-methyl-phenyl)-5-*tert*-butyl-2H-pyrazole-3-yl, B is naphthyl, L is -O-(CH<sub>2</sub>)<sub>2</sub>- and M is morpholine, which releases 1-(5-*tert*-butyl-2-(4-methyl-phenyl)-2H-pyrazole-3-yl)-3-[4-(2-morpholinylethoxy)naphthalene-1-yl]urea (BIRB 796) as an active ingredient.

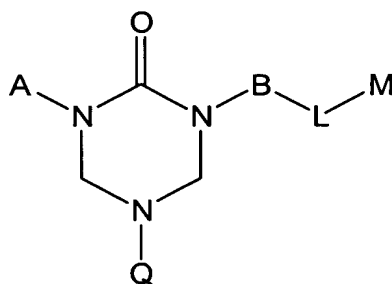
36. A method for treating or preventing inflammatory and immunomodulatory diseases, such as rheumatoid arthritis, osteoarthritis, psoriasis, acute rheumatic fever, sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Crohn's disease, ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases, chronic obstructive pulmonary disease, septic arthritis, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, and temporomandibular joint disease, comprising administering a compound of formula I wherein A is 2-(4-methyl-phenyl)-5-*tert*-butyl-2H-pyrazole-3-yl, B is naphthyl, L is -O-(CH<sub>2</sub>)<sub>2</sub>- and M is morpholine, which releases 1-(5-*tert*-butyl-2-(4-methyl-phenyl)-

2H-pyrazole-3-yl)-3-[4-(2-morpholinylethoxy)naphthalene-1-yl]urea (BIRB 796) as an active ingredient.

37. A method for treating or preventing a disease which is a VEGF mediated disorder which comprises administering a compound of Formula I, a salt form of a compound of Formula I, or an isomer of a compound of claim 1.

38. A method for regulating the *tyrosine kinase* signal transduction comprising administering to a human or other mammal a compound of claim 1.

39. A compound of formula I:



or a pharmaceutically acceptable salt thereof,

wherein

A of formula I is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_pR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro;

B is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_5$  linear or branched haloalkyl up to perhalo,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy up to per haloalkoxy, hydroxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

L is -O- or -S-,

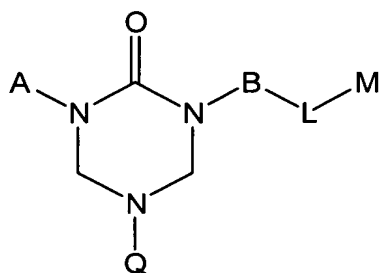
M is phenyl, pyridine, quinoline, morpholine, indazole, isoquinoline, pyrimidine, or benzimidazole, optionally substituted with 1-3 substituents independently selected from the group consisting of R<sup>4</sup>, OR<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>, S(O)<sub>q</sub>R<sup>4</sup>, SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, C(O)NR<sup>4</sup>R<sup>5</sup>, C(NR<sup>4</sup>)R<sup>5</sup>, NR<sup>4</sup>SO<sub>2</sub>R<sup>5</sup>, C(O)R<sup>4</sup>, C(O)OR<sup>4</sup>, NR<sup>4</sup>C(O)R<sup>5</sup>, NR<sup>4</sup>C(O)OR<sup>5</sup>, halogen, cyano, and nitro;

each R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>5</sup> and Q is independently selected from the group consisting of:

- (a) hydrogen,
  - (b) C<sub>1</sub>-C<sub>5</sub> linear, branched, or cyclic alkyl,
  - (c) C<sub>1</sub>-C<sub>5</sub> linear or branched hydroxy alkyl,
  - (d) C<sub>1</sub>-C<sub>5</sub> linear or branched alkoxy substituted - C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl,
  - (e) phenyl,
  - (f) pyridinyl
  - (g) C<sub>1</sub>-C<sub>3</sub> alkyl-phenyl,
  - (h) C<sub>1</sub>-C<sub>3</sub> alkyl-pyridinyl or
  - (i) up to per-halo substituted C<sub>1</sub>-C<sub>5</sub> linear, branched or cyclic alkyl and
- the variables p and q are integers independently selected from 0, 1, or 2.

40. A compound of claim 39 wherein, M is phenyl or pyridine.

41. A compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein

A of formula I is pyridinyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_pR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro;

B is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_5$  linear or branched haloalkyl up to perhalo,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy up to per haloalkoxy, hydroxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

L is -O- or -S-,

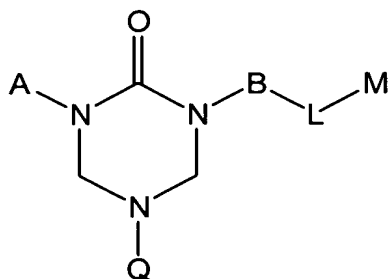
M is phenyl, pyridine, quinoline, morpholine, indazole, isoquinoline, pyrimidine, or benzimidazole, optionally substituted with 1-3 substituents which independently are  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, or nitro;

each  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$  and Q is independently :

- (a) hydrogen,
  - (b)  $C_1$ - $C_5$  linear, branched, or cyclic alkyl,
  - (c)  $C_1$ - $C_5$  linear or branched hydroxy alkyl,
  - (d)  $C_1$ - $C_5$  linear or branched alkoxy substituted -  $C_1$ - $C_5$  linear or branched alkyl,
  - (e) phenyl,
  - (f) pyridinyl
  - (g)  $C_1$ - $C_3$  alkyl-phenyl,
  - (h)  $C_1$ - $C_3$  alkyl-pyridinyl or
  - (i) up to per-halo substituted  $C_1$ - $C_5$  linear, branched or cyclic alkyl and
- the variables p and q are integers independently selected from 0, 1, or 2.

42. A compound of claim 41 wherein M is phenyl or pyridine.

43. A compound of formula I,



or a pharmaceutically acceptable salt thereof,

wherein

A of formula I is pyrazole, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_pR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro;

B is phenyl or naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_5$  linear or branched haloalkyl up to perhalo,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy up to per haloalkoxy, hydroxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

L is  $-O-$  or  $-S-$ ,

M is phenyl, pyridine, quinoline, morpholine, indazole, isoquinoline, pyrimidine, or benzimidazole, optionally substituted with 1-3 substituents which independently are  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, or nitro;

each  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$  and Q is independently :

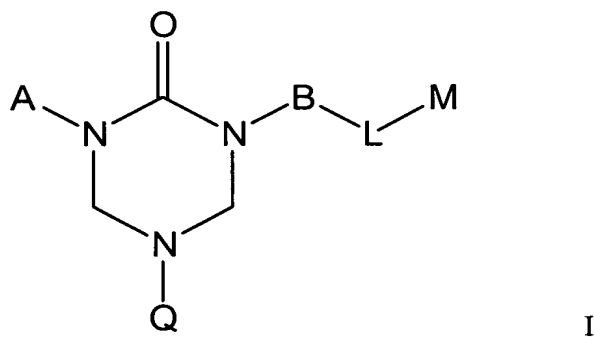
- (a) hydrogen,
- (b)  $C_1$ - $C_5$  linear, branched, or cyclic alkyl,
- (c)  $C_1$ - $C_5$  linear or branched hydroxy alkyl,



- (d) C<sub>1</sub>-C<sub>5</sub> linear or branched alkoxy substituted - C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl,
- (e) phenyl,
- (f) pyridinyl
- (g) C<sub>1</sub>-C<sub>3</sub> alkyl-phenyl,
- (h) C<sub>1</sub>-C<sub>3</sub> alkyl-pyridinyl or
- (i) up to per-halo substituted C<sub>1</sub>-C<sub>5</sub> linear, branched or cyclic alkyl and the variables p and q are integers independently selected from 0, 1, or 2.

44. A compound of claim 43 wherein M is phenyl or pyridine.

45. A compound of formula I,



or a pharmaceutically acceptable salt thereof,

wherein

A is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R<sup>1</sup>, OR<sup>1</sup> and halogen;

B is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl, C<sub>1</sub>-C<sub>5</sub> linear or branched haloalkyl up to perhalo, C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> haloalkoxy up to per haloalkoxy, hydroxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>6</sub> dialkylamino, halogen, cyano, and nitro;

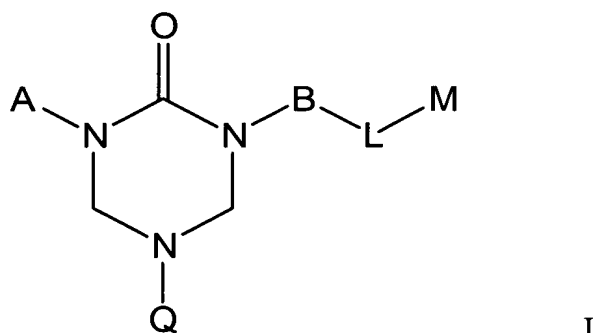
L is -O- or -S-:

M is pyridinyl, optionally with 1-3 substituents independently selected from the group consisting R<sup>4</sup>, OR<sup>4</sup>, NR<sup>4</sup>R<sup>5</sup>, S(O)<sub>q</sub>R<sup>4</sup>, SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, C(O)NR<sup>4</sup>R<sup>5</sup>, C(NR<sup>4</sup>)R<sup>5</sup>, NR<sup>4</sup>SO<sub>2</sub>R<sup>5</sup>, C(O)R<sup>4</sup>, C(O)OR<sup>4</sup>, NR<sup>4</sup>C(O)R<sup>5</sup>, NR<sup>4</sup>C(O)OR<sup>5</sup>, halogen, cyano, nitro and oxides;

each R<sup>4</sup>, R<sup>5</sup> and Q is independently :

- (a) hydrogen,
- (b) C<sub>1</sub>-C<sub>5</sub> linear, branched, or cyclic alkyl,
- (c) C<sub>1</sub>-C<sub>5</sub> linear or branched hydroxy alkyl,
- (d) C<sub>1</sub>-C<sub>5</sub> linear or branched alkoxy substituted - C<sub>1</sub>-C<sub>5</sub> linear or branched alkyl,
- (e) phenyl,
- (f) pyridinyl,
- (g) C<sub>1</sub>-C<sub>3</sub> alkyl-phenyl,
- (h) C<sub>1</sub>-C<sub>3</sub> alkyl-pyridinyl or
- (i) up to per-halo substituted C<sub>1</sub>-C<sub>5</sub> linear, branched or cyclic alkyl and the variables p and q are integers independently selected from 0, 1, or 2.

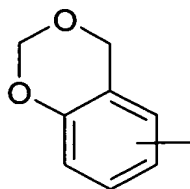
46. A compound of formula I,



or a pharmaceutically acceptable salt thereof,

wherein

A is of the formula X:



X

where A is optionally substituted with 1-4 substituents independently selected from the group consisting of  $R^1$ ,  $OR^1$ ,  $NR^1R^2$ ,  $S(O)_pR^1$ ,  $SO_2NR^1R^2$ ,  $NR^1SO_2R^2$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $C(O)NR^1R^2$ ,  $NR^1C(O)R^2$ ,  $NR^1C(O)OR^2$ , halogen, cyano, and nitro,

B is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $C_1$ - $C_5$  linear or branched alkyl,  $C_1$ - $C_5$  linear or branched haloalkyl up to perhalo,  $C_1$ - $C_3$  alkoxy,  $C_1$ - $C_3$  haloalkoxy up to per haloalkoxy, hydroxy, amino,  $C_1$ - $C_3$  alkylamino,  $C_1$ - $C_6$  dialkylamino, halogen, cyano, and nitro;

L is -O- or -S-:

M is :

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, and nitro; or

(ii) pyridinyl optionally with 1-3 substituents independently selected from the group consisting  $R^4$ ,  $OR^4$ ,  $NR^4R^5$ ,  $S(O)_qR^4$ ,  $SO_2NR^4R^5$ ,  $C(O)NR^4R^5$ ,  $C(NR^4)R^5$ ,  $NR^4SO_2R^5$ ,  $C(O)R^4$ ,  $C(O)OR^4$ ,  $NR^4C(O)R^5$ ,  $NR^4C(O)OR^5$ , halogen, cyano, nitro and oxides;

where  $R^4$ ,  $R^5$  and Q are independently :

- (a) hydrogen,
- (b)  $C_1$ - $C_5$  linear, branched, or cyclic alkyl,
- (c)  $C_1$ - $C_5$  linear or branched hydroxy alkyl,
- (d)  $C_1$ - $C_5$  linear or branched alkoxy substituted -  $C_1$ - $C_5$  linear or branched alkyl,
- (e) phenyl,

(f) up to per-halo substituted C<sub>1</sub>-C<sub>5</sub> linear, branched or cyclic alkyl,  
and the variables p and q are integers independently selected from 0, 1, or 2.